#5

```
Met Asp Trp Pro His Asn Leu Leu Phe Leu Leu Thr Ile Ser Ile
  1               5                  10                  15

Phe Leu Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys
                 20                  25                  30

Gly Gln Gly Arg Pro Gly Pro Leu Ala Pro Gly Pro His Gln Val
                 35                  40                  45

Pro Leu Asp Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu
                 50                  55                  60

Glu Tyr Glu Arg Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn
                 65                  70                  75

Ser Ser Glu Leu Ala Gln Arg Lys Cys Glu Val Asn Leu Gln Leu
                 80                  85                  90

Trp Met Ser Asn Lys Arg Ser Leu Ser Pro Trp Gly Tyr Ser Ile
                 95                 100                 105

Asn His Asp Pro Ser Arg Ile Pro Val Asp Leu Pro Glu Ala Arg
                110                 115                 120

Cys Leu Cys Leu Gly Cys Val Asn Pro Phe Thr Met Gln Glu Asp
                125                 130                 135

Arg Ser Met Val Ser Val Pro Val Phe Ser Gln Val Pro Val Arg
                140                 145                 150

Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr Gly Pro Cys Arg Gln
                155                 160                 165

Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys Thr Cys Ile Phe
                170                 175                 180
```

FIG. 1

aggcgggcag cagctgcagg ctgaccttgc agcttggcgg aatggactgg 50

cctcacaacc tgctgtttct tcttaccatt tccatcttcc tggggctggg 100

ccagcccagg agccccaaaa gcaagaggaa ggggcaaggg cggcctgggc 150

ccctggcccc tggccctcac caggtgccac tggacctggt gtcacggatg 200

aaaccgtatg cccgcatgga ggagtatgag aggaacatcg aggagatggt 250

ggcccagctg aggaacagct cagagctggc ccagagaaag tgtgaggtca 300

acttgcagct gtggatgtcc aacaagagga gcctgtctcc ctggggctac 350

agcatcaacc acgaccccag ccgtatcccc gtggacctgc cggaggcacg 400

gtgcctgtgt ctgggctgtg tgaacccctt caccatgcag gaggaccgca 450

gcatggtgag cgtgccggtg ttcagccagg ttcctgtgcg ccgccgcctc 500

tgcccgccac cgccccgcac agggccttgc cgccagcgcg cagtcatgga 550

gaccatcgct gtgggctgca cctgcatctt ctgaatcacc tggcccagaa 600

gccaggccag cagcccgaga ccatcctcct tgcacctttg tgccaagaaa 650

ggcctatgaa aagtaaacac tgacttttga aagcaag 687

FIG. 2

Met Thr Leu Leu Pro Gly Leu Leu Phe Leu Thr Trp Leu His Thr
1 5 10 15

Cys Leu Ala His His Asp Pro Ser Leu Arg Gly His Pro His Ser
20 25 30

His Gly Thr Pro His Cys Tyr Ser Ala Glu Glu Leu Pro Leu Gly
35 40 45

Gln Ala Pro Pro His Leu Leu Ala Arg Gly Ala Lys Trp Gly Gln
50 55 60

Ala Leu Pro Val Ala Leu Val Ser Ser Leu Glu Ala Ala Ser His
65 70 75

Arg Gly Arg His Glu Arg Pro Ser Ala Thr Thr Gln Cys Pro Val
80 85 90

Leu Arg Pro Glu Glu Val Leu Glu Ala Asp Thr His Gln Arg Ser
95 100 105

Ile Ser Pro Trp Arg Tyr Arg Val Asp Thr Asp Glu Asp Arg Tyr
110 115 120

Pro Gln Lys Leu Ala Phe Ala Glu Cys Leu Cys Arg Gly Cys Ile
125 130 135

Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala Leu Asn Ser Val Arg
140 145 150

Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg Pro Cys Ser Arg
155 160 165

Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala Phe His Thr
170 175 180

Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu Pro Arg
185 190 195

Ser Val
197

FIG. 3

gccaggtgtg caggccgctc caagcccagc ctgccccgct gccgccacca 50
tgacgctcct ccccggcctc ctgtttctga cctggctgca cacatgcctg 100
gcccaccatg acccctccct caggggcac ccccacagtc acggtacccc 150
acactgctac tcggctgagg aactgcccct cggccaggcc cccccacacc 200
tgctggctcg aggtgccaag tgggggcagg ctttgcctgt agccctggtg 250
tccagcctgg aggcagcaag ccacaggggg aggcacgaga ggccctcagc 300
tacgacccag tgcccggtgc tgcggccgga ggaggtgttg gaggcagaca 350
cccaccagcg ctccatctca ccctggagat accgtgtgga cacggatgag 400
gaccgctatc cacagaagct ggccttcgcc gagtgcctgt gcagaggctg 450
tatcgatgca cggacgggcc gcgagacagc tgcgctcaac tccgtgcggc 500
tgctccagag cctgctggtg ctgcgccgcc ggccctgctc ccgcgacggc 550
tcggggctcc ccacacctgg ggcctttgcc ttccacaccg agttcatcca 600
cgtccccgtc ggctgcacct gcgtgctgcc ccgttcagtg tgaccgccga 650
ggccgtgggg cccctagact ggacacgtgt gctccccaga gggcaccccc 700
tatttatgtg tatttattgt tatttatatg cctcccccaa cactaccctt 750
ggggtctggg cattccccgt gtctggagga cagcccccca ctgttctcct 800
catctccagc ctcagtagtt gggggtagaa ggagctcagc acctcttcca 850
gcccttaaag ctgcagaaaa ggtgtcacac ggctgcctgt accttggctc 900
cctgtcctgc tcccggcttc ccttacccta tcactggcct caggccccgc 950
aggctgcctc ttcccaacct ccttggaagt acccctgttt cttaaacaat 1000
tatttaagtg tacgtgtatt attaaactga tgaacacatc cccaaaa 1047

FIG. 4

ggcagcaggg accaagagag gcacgcttgc ccttttatga catcagagct 50

cctggttctt gctccttggg actctgggac ttacaccagt ggcacccctg 100

gctcnnnnnn nnnnnaattc ggtacgaggc tggggttcag gcgggcagca 150

gctgcaggct gaccttgcag cttggcggaa tggactggcc tcacaacctg 200

ctgtttcttc ttaccatttc catcttcctg gggctgggcc agcccaggag 250

ccccaaaagc aagaggaagg ggcaagggcg gcctgggccc ctggtccctg 300

gccctcacca ggtgccactg gacctggtgt cacggatgaa accgtatgcc 350

cgcatggagg agtatgagag gaacatcgag gagatgttgg cccagctgag 400

gaacagttca gagctggccc agagaaagtg tgaggtcaac ttgcagctgt 450

ggatgtccaa caagaggagc ctgtctccct ggggctacag catcaaccac 500

gaccccagcc gtatccccgt ggacctccgg aggcacggtg cctgtgtctg 550

ggcttgtgtg aacccсttca ccatgcagga ggaccgcagc atggtgagcg 600

tgccggtgtt cagccaggtt cctgtgcgcc gccgcctctg cccgccaccg 650

ccccgcacag ggccttgccg ccagcgcgca gtcatggaga ccatcgctgt 700

gggctgcacc tgcatcttct gaatcgacct ggcccagaag ccaggccagc 750

agcccgagac catcctcctt gcacctttgt gccaagaaag gcctatgaaa 800

agtaaacact gacttttgaa agcaaaaaaa 830

FIG. 5

cacggatgag gaccgctatc cacagaagct ggccttcgcc gagtgcctgt 50

gcagaggctg tatcgatgca cggacgggcc gcgagacagc tgcgctcaac 100

tccgtgcggc tgctccagag cctgctggtg ctgcgccgcc ggccctgctc 150

ccgcgacggc tcggggctcc ccacacctgg ggcctttgcc ttccacaccg 200

agttcatcca cgtccccgtc ggctgcacct 230

FIG. 6

```
hIL17     1   ...................................MTPGKTSLVSLLLLL
hIL17B    1   ........MDWPHNLLFLLTISIFLGLGQPRSPKSKRKGQGRPGPLAPGP
hIL17C    1   MTLLPGLLFLTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPH

hIL17     16  SLEAIVKAGITIPRNPGCPNSEDKNFPRTVMVNLNIHNRNTNTNPKRSSD
hIL17B    43  HQVPLDLVSRMKPYARMEEYERNIEEMVAQLRNSSELAQRKCEVNLQLWM
hIL17C    51  LLARGAKWGQALPVALVSSLEAASHRGRHERPSATTQCPVLRPEEVLEAD

                      *                   *     *
hIL17     66  YYNRSTSPWNLHRNEDPERYPSVIWEAKCRHLGCINADGNVDYHMNSVPI
hIL17B    93  SNKRSLSPWGYSINHDPSRIPVDLPEARCLCLGCVNPFTMQEDRSMVSVP
hIL17C    101 THQRSISPWRYRVDTDEDRYPQKLAFAECLCRGCIDARTGRETAALNSVR

                            *                        *  *
hIL17     116 QQEI·LVLRREPPHCPNS···········FRLEKILVSVGCTCVTPIVHHVA
hIL17B    143 VFSQVPVRRRL···CPPPPRT····GPCRQRAVMETIAVGCTCIF········
hIL17C    151 LLQSLLVLRRRP··CSRDGSGLPTPGAFAEHTEFIHVPVGCTCVLPRSV···
```

FIG. 7A

```
59294    1  M D W P H N L L F L L T I S I F L G L G Q P R S P K S K R K G Q G R P G P L A P G P - - - H Q V P L
62377    1  M T L L P G L L F L T W L H T C L A H H D P - S L R G H P H S H G T P H C Y S A E E L P L G Q A P P

59294   48  D L V S R M K P Y A R M - - E E Y E R N I E E M V A Q L R N S S E L A Q R K C E V - - - - N L Q L W
62377   50  H L L A R G A K W G Q A L P V A L V S S L E A A S H R G R H E R P S A T T Q C P V L R P E E V L E A

59294   92  M S N K R S L S P W G Y S I N H D P S R I P V D L P E A R C L C L G C V N P F T M Q E D R S M V S V
62377  100  D T H Q R S I S P W R Y R V D T D E D R Y P Q K L A F A E C L C R G C I D A R T G R E T A A L N S V

59294  142  P V F - S Q V P V R R R L C P P P - - - - P R T G P C R Q R A V M E T I A V G C T C I F
62377  150  R L L Q S L L V L R R R P C S R D G S G L P T P G A F A F H T E F I H V P V G C T C V L P R S V
```

FIG. 7B

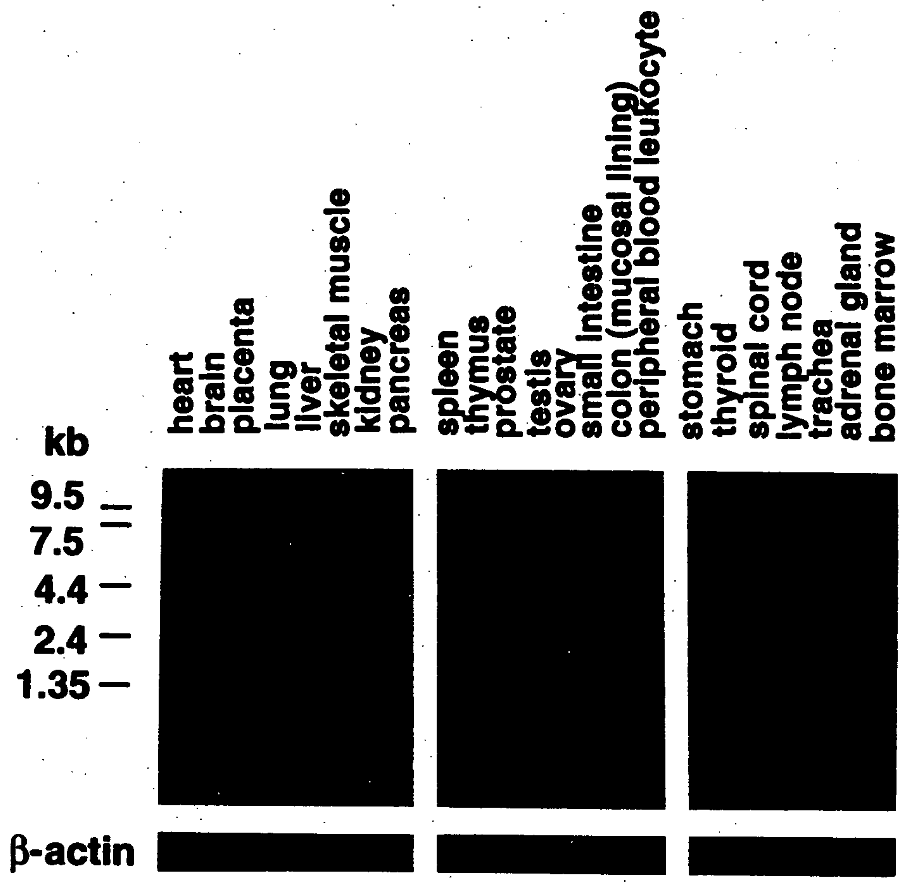

heart
brain
placenta
lung
liver
skeletal muscle
kidney
pancreas
spleen
thymus
prostate
testis
ovary
small intestine
colon (mucosal lining)
peripheral blood leukocyte
stomach
thyroid
spinal cord
lymph node
trachea
adrenal gland
bone marrow
kb
9.5
7.5
4.4
2.4
1.35
β-actin

FIG. 8

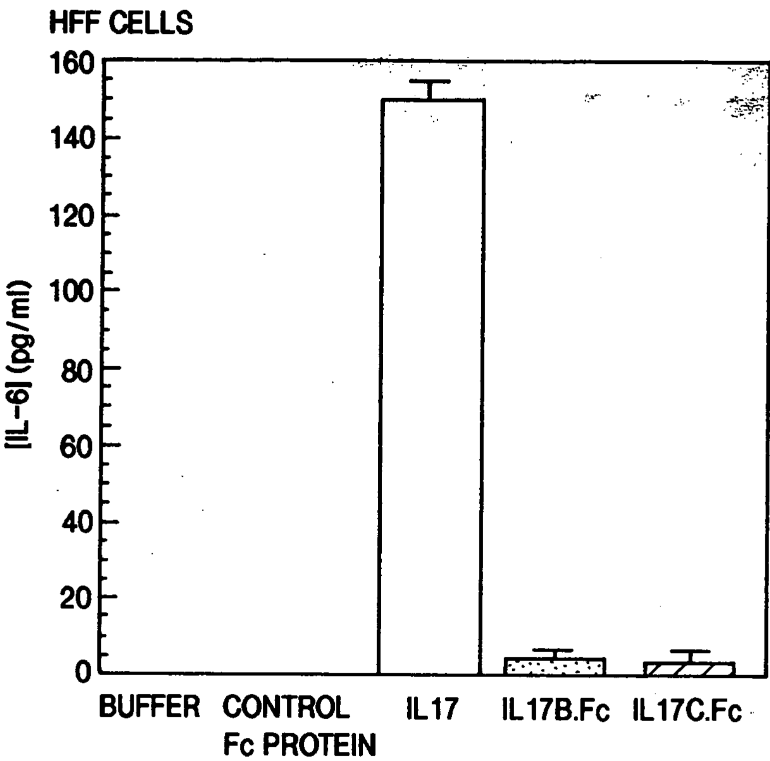

HFF CELLS
160
140
120
100
80
60
40
20
0
[IL-6] (pg/ml)
BUFFER
CONTROL
Fc PROTEIN
IL17
IL17B.Fc
IL17C.Fc

FIG. 9A

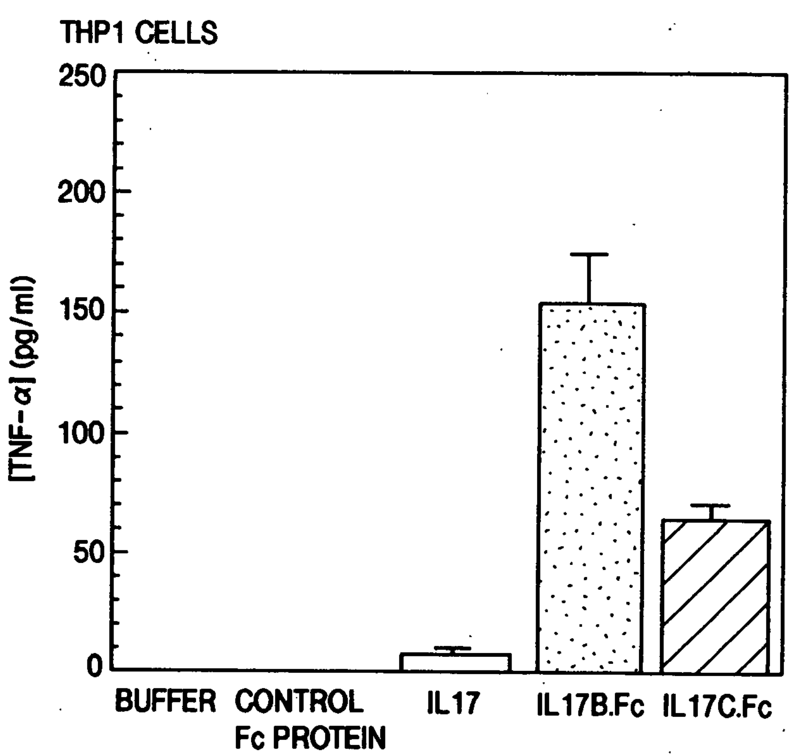

THP1 CELLS
250
200
150
100
50
0
[TNF-α] (pg/ml)
BUFFER
CONTROL
Fc PROTEIN
IL17
IL17B.Fc
IL17C.Fc

FIG. 9B

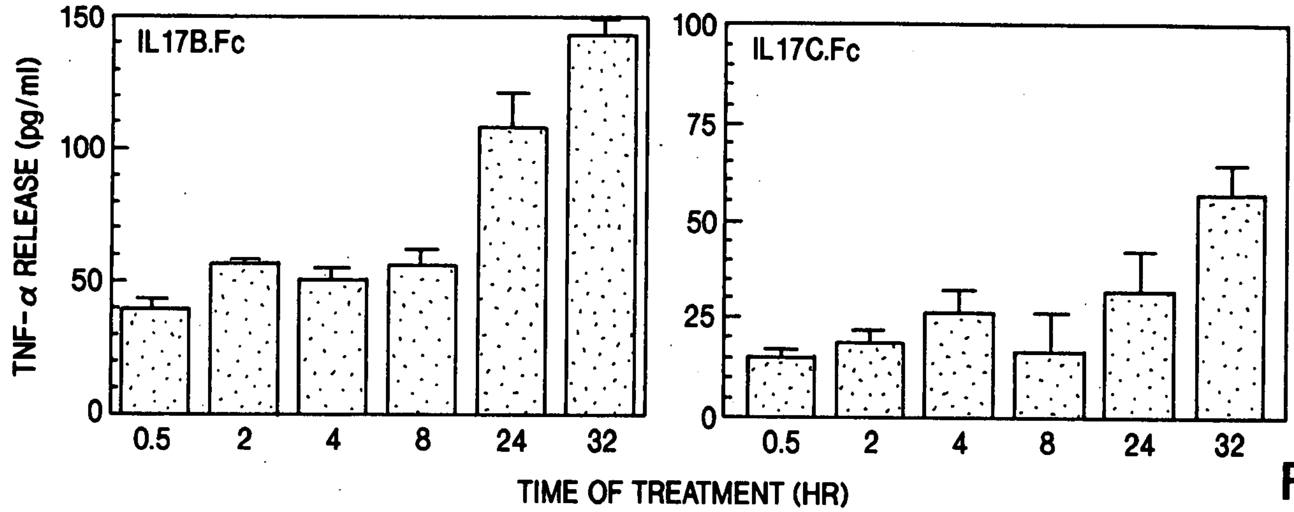


FIG. 10A

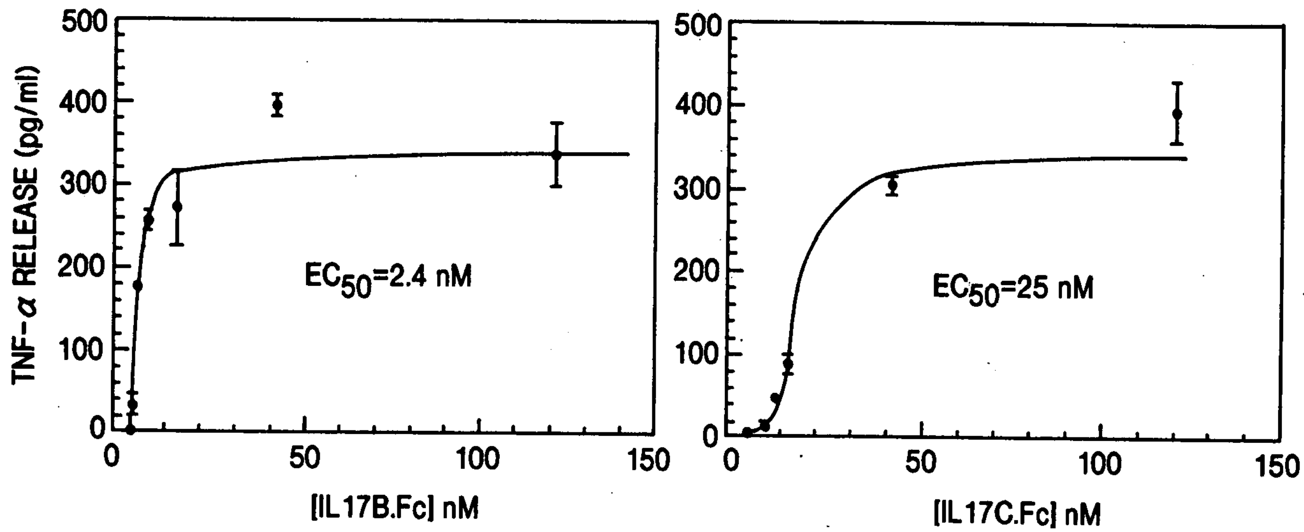


FIG. 10B

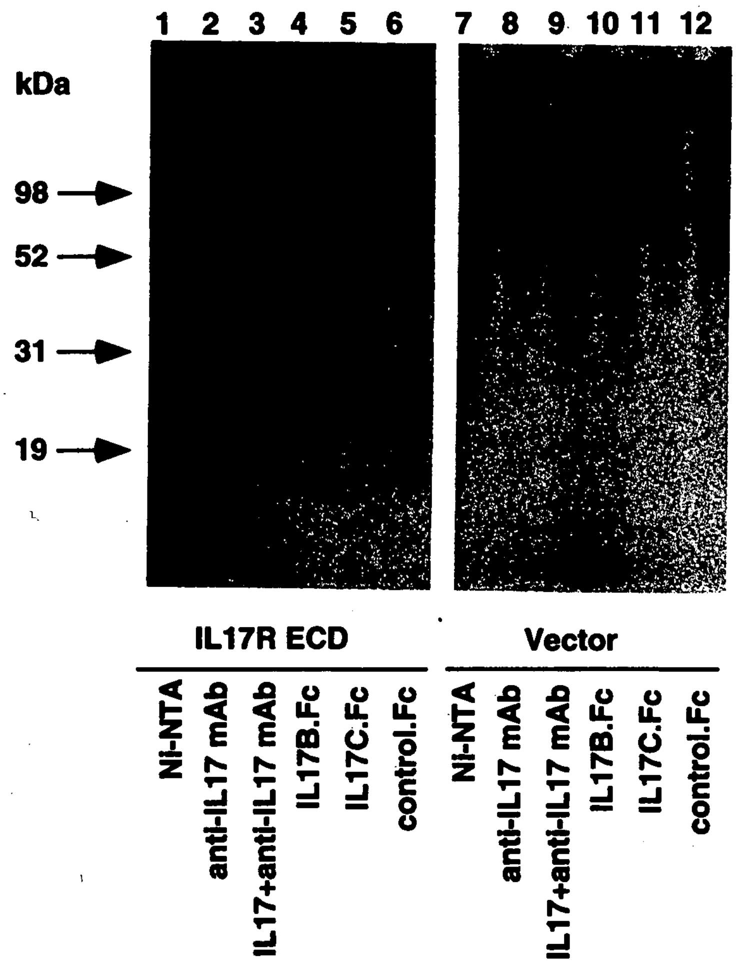


FIG. 11A

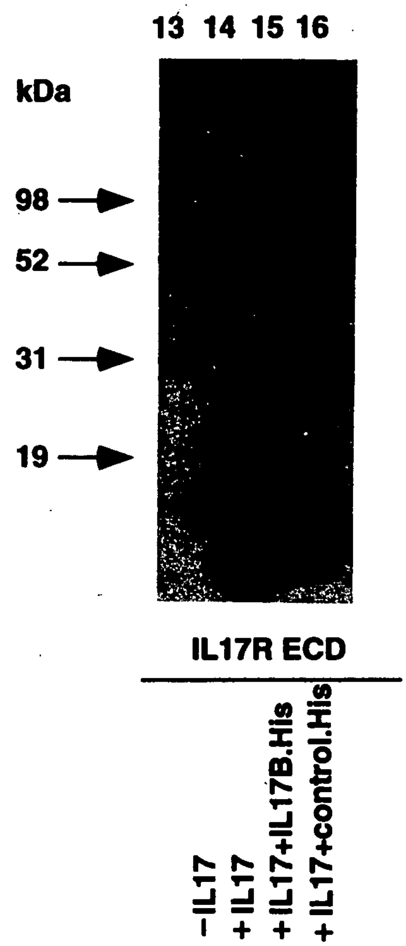


FIG. 11B

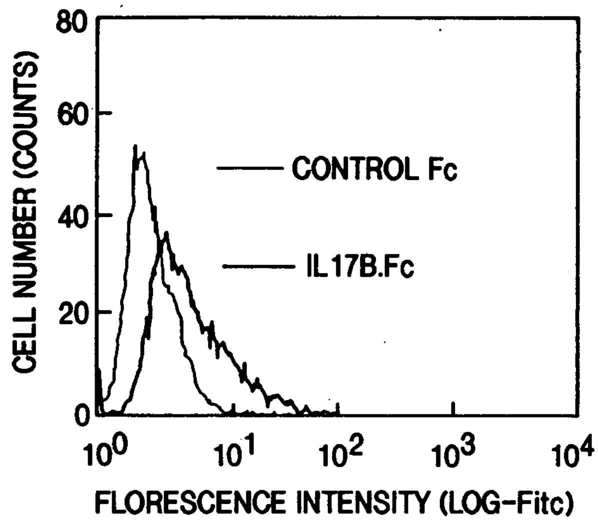


FIG. 12A

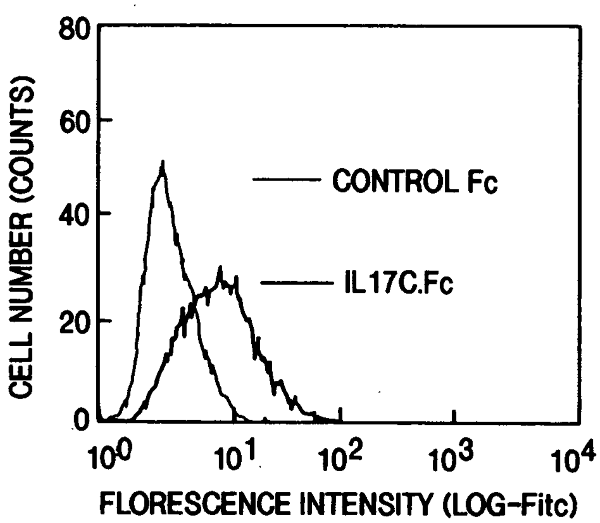
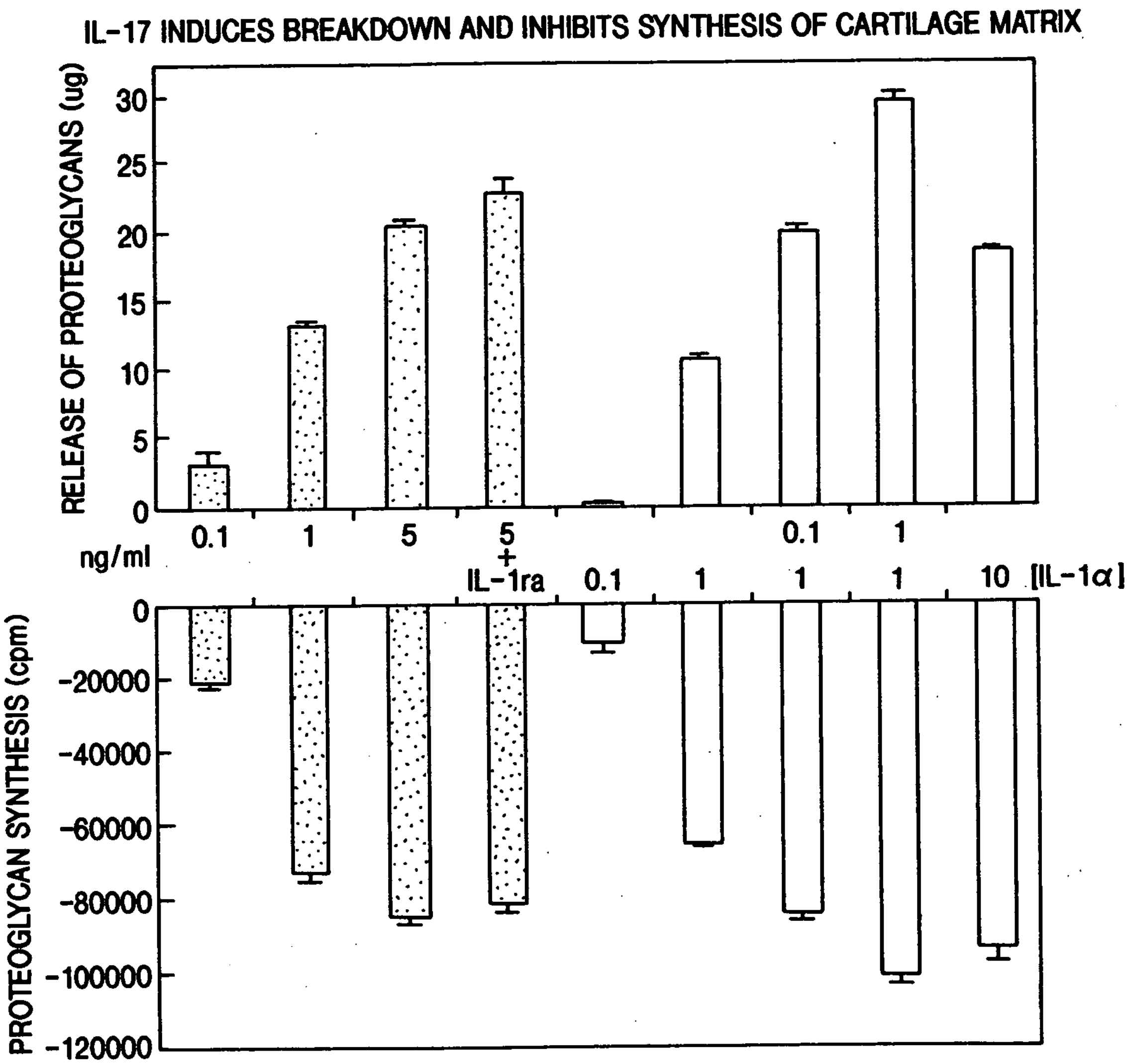


FIG. 12B



IL-17 INDUCES BREAKDOWN AND INHIBITS SYNTHESIS OF CARTILAGE MATRIX
RELEASE OF PROTEOGLYCANS (ug)
0
5
10
15
20
25
30
ng/ml
0.1
1
5
5
+
IL-1ra
0.1
1
0.1
1
1
1
10
[IL-1α]
PROTEOGLYCAN SYNTHESIS (cpm)
0
-20000
-40000
-60000
-80000
-100000
-120000

FIG. 13

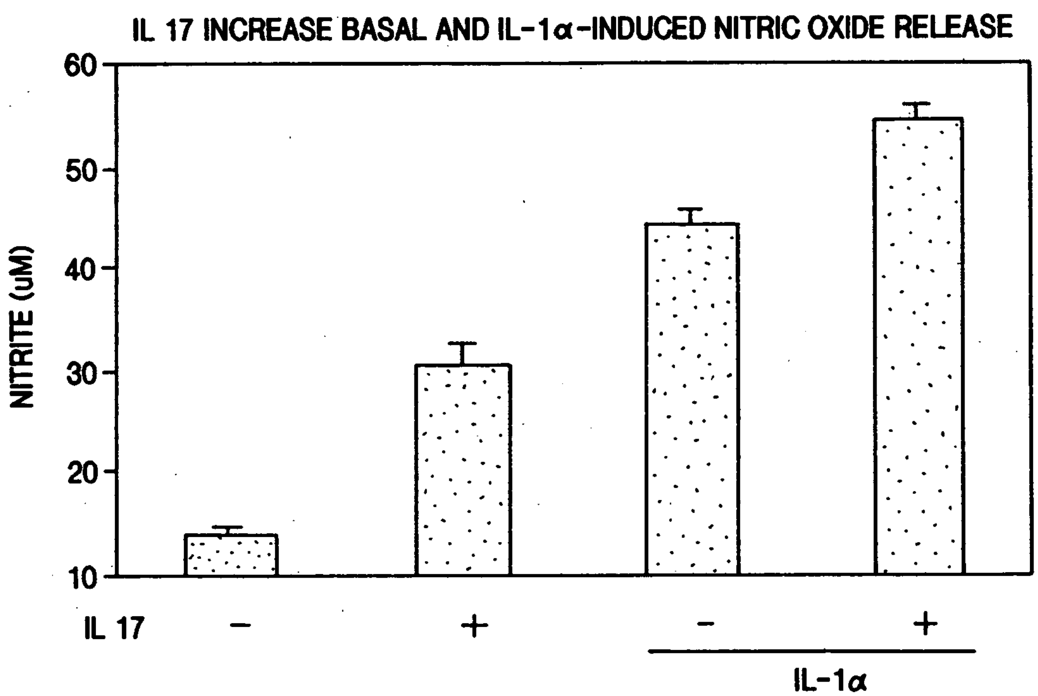

IL 17 INCREASE BASAL AND IL-1α-INDUCED NITRIC OXIDE RELEASE
NITRITE (uM)
60
50
40
30
20
10
IL 17
−
+
−
+
IL-1α

FIG. 14

INHIBITION OF NITRIC OXIDE RELEASE DOES NOT BLOCK THE DETRIMENTAL EFFECTS OF IL 17 ON MATRIX BREAKDOWN OR SYNTHESIS

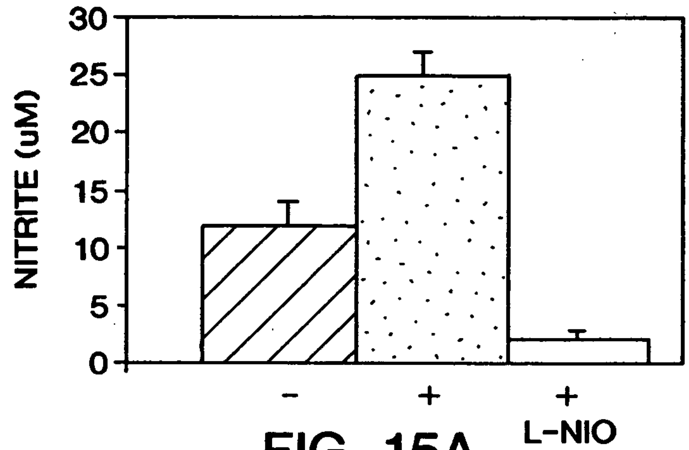


FIG. 15A

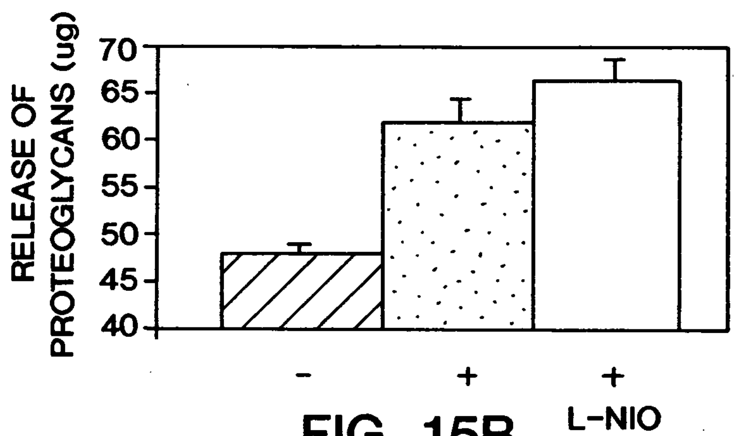


FIG. 15B

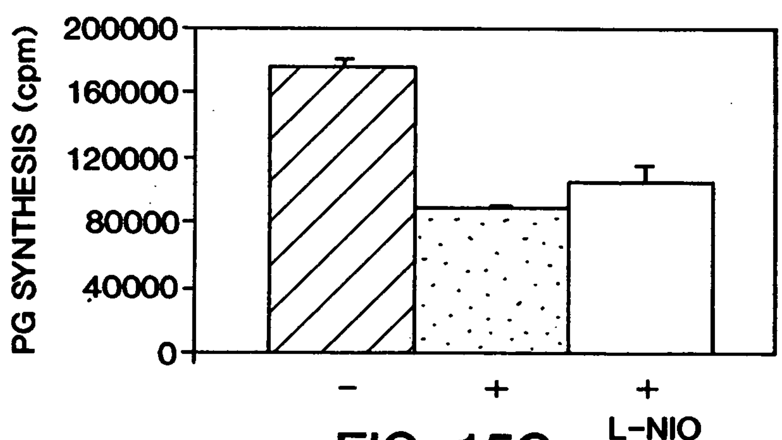


FIG. 15C

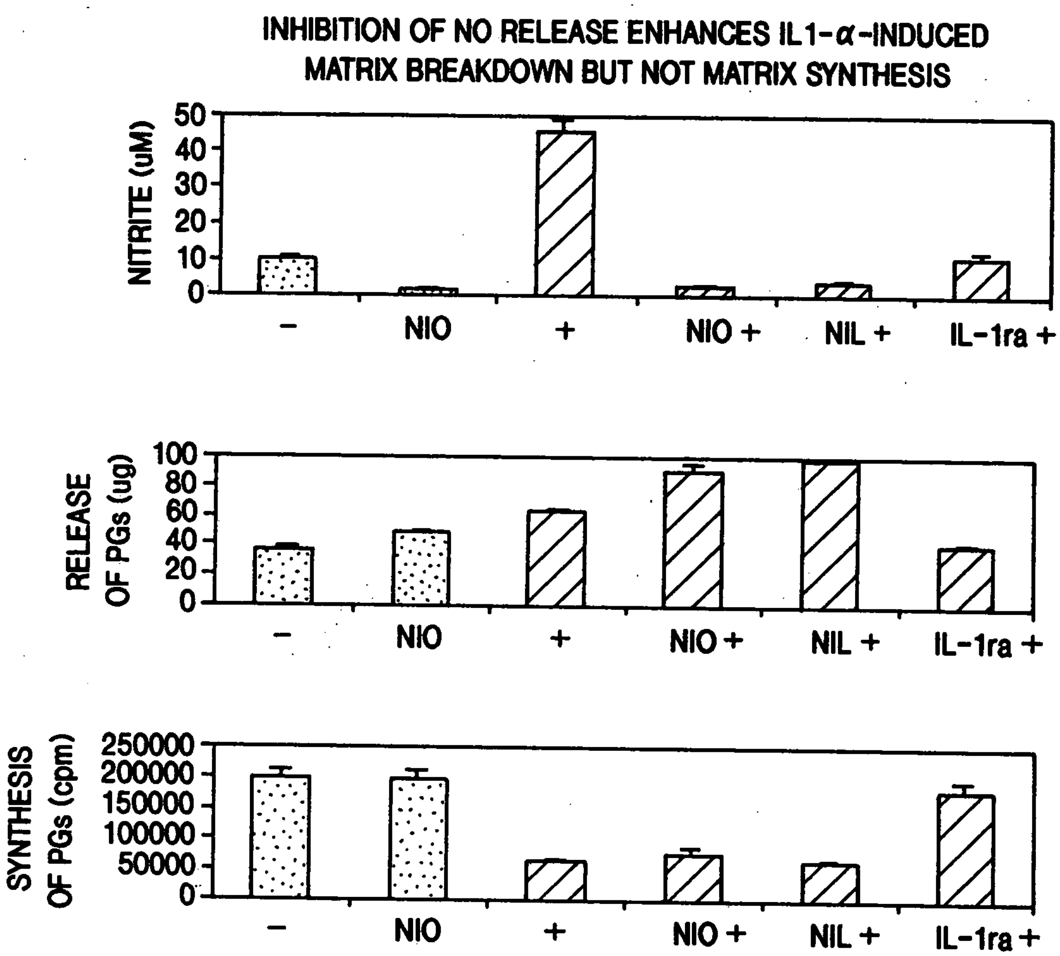

INHIBITION OF NO RELEASE ENHANCES IL1-α-INDUCED
MATRIX BREAKDOWN BUT NOT MATRIX SYNTHESIS
NITRITE (uM)
50
40
30
20
10
0
-
NIO
+
NIO +
NIL +
IL-1ra +
RELEASE OF PGs (ug)
100
80
60
40
20
0
-
NIO
+
NIO +
NIL +
IL-1ra +
SYNTHESIS OF PGs (cpm)
250000
200000
150000
100000
50000
0
-
NIO
+
NIO +
NIL +
IL-1ra +

FIG. 16

IL 17 HOMOLOGUE 1 (UNQ 516) HAS POSITIVE EFFECTS ON ARTICULAR CARTILAGE

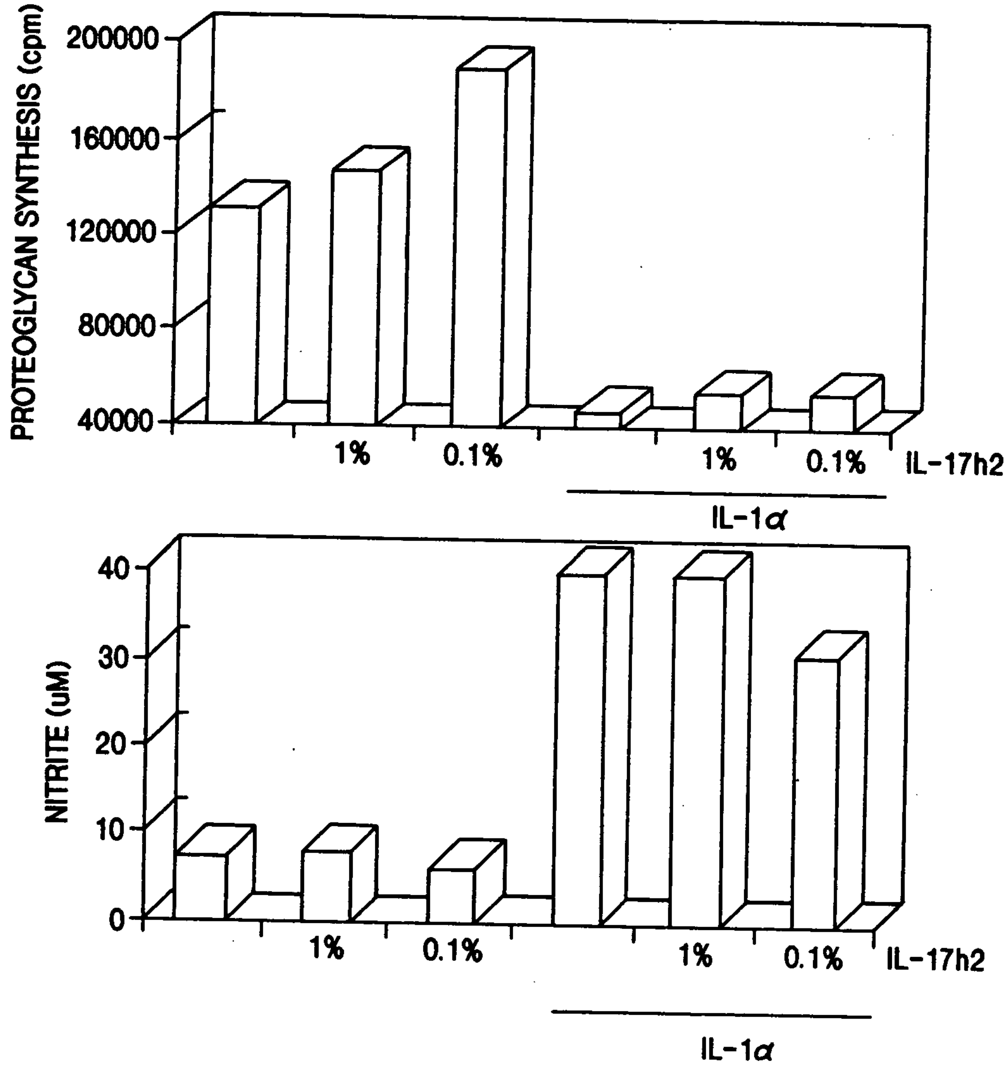


FIG. 17

IL 17 HOMOLOGUE (UNQ 561) HAS DETRIMENTAL EFFECTS ON ARTICULAR CARTILAGE

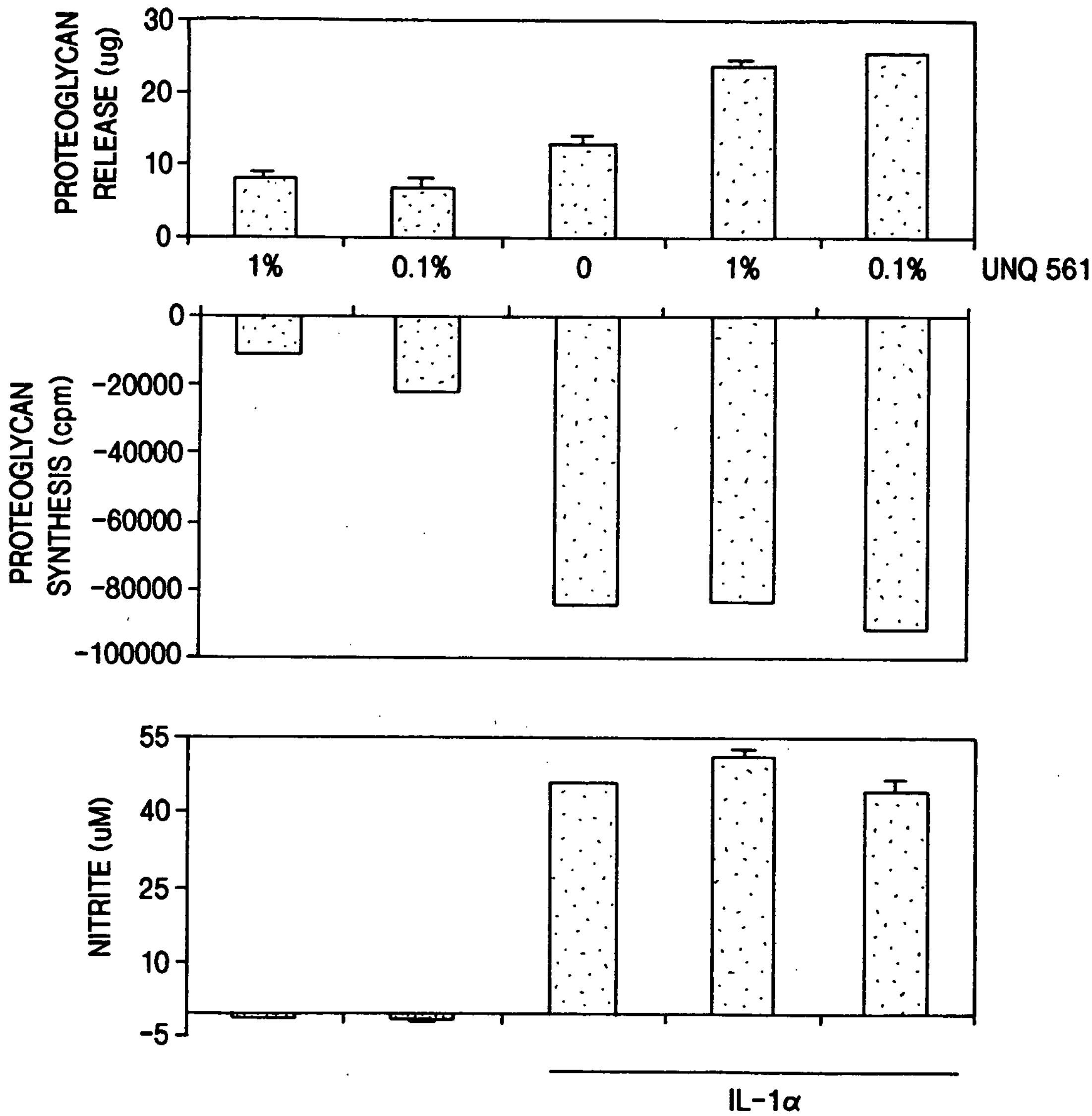


FIG. 18